Amendments to the Specification:

Please replace originally-filed pages 8-10, 8a, 9a, and 10a, with the following amended text:

DESCRIPTION OF THE INVENTION

This invention refers to the use of an adenovirus defective in its VAI and VAII virus-associated RNAs ~~for the production of a pharmaceutical composition~~ for the treatment of cancer.

It also refers to the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus has a mutation in the sequences of the VAI and VAII RNA genes.

Another objective of the invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus has a mutation in the sequences of the genes that control the expression of the VAI and VAII RNA genes.

Another objective of the invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus has mutations in the VA RNA genes in one or more genes of the group Ela, Elb, and E4 to obtain selective replication in tumors.

Another objective of the invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus has mutations in the VA RNA genes and promoters that regulate one or more genes in the group Ela, Elb, and E4 to obtain selective replication in tumors.

Yet another objective of this invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus has mutations in the VA RNA genes to obtain selective replication in tumor cells with an active Ras pathway or unresponsive to the action of interferon.

Yet another objective of this invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus has mutations in

the VA RNA genes to obtain selective replication in tumor cells and modifications in its capsid to increase its infectivity or to direct it to a receptor present on a tumor cell.

Yet another objective of this invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus has mutations in the VA RNA genes that confer selective replication on tumor cells and that, in turn, contain other genes commonly used in the field of cancer gene therapy such as prodrug activators, tumor suppressors, or immunostimulants.

Yet another objective of this invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus is a human adenovirus derived from a serotype between 1 and 50 with genetic mutations in the VA RNAs genes that confer selective replication on tumor cells.

Yet another objective of this invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus is a human adenovirus derived from serotype 5.

Yet another objective of this invention is the use of an adenovirus ~~for the production of a pharmaceutical composition~~ for the treatment of cancer wherein said adenovirus is a mutant adenovirus d1331.

This invention describes the use of mutant adenoviruses from VA RNA genes in cancer treatment. The VA RNA mutation allows replication of the adenovirus subject to the existence of an active Ras pathway or on the lack of PKR activation due to insensitivity to interferon. The invention is aimed at the need to find better treatments for pancreatic cancer, colon cancer, lung cancer, and other types of tumors.

This invention comprises adenoviruses that contain mutations in their genome that eliminate the PKR inactivating function of the associated-virus (VA) RNAs. There are two genes that encode VA RNAs in the genome of the adenovirus, VAI and VAII, located at approximately 30 map units on the viral genome. Both produce a short RNA (of some 160 ribonucleotides) synthesized by an RNA-polymerase III in the late phase of the viral cycle. Each VA RNA is folded in the shape of a loop that is bound to an RNA-dependent kinase, PKR. For

the purpose of propagation, the adenovirus uses the VA RNAs to inhibit PKR, since otherwise this kinase phosphorylates the translation factor of eIF2 proteins, inactivating it and blocking protein. synthesis overall. Therefore, the VA mutants described in this invention are poorly propagated in normal cells. Conversely, these mutants are propagated normally in cells where the PKR is inactivated by the Ras pathway, as happens in many tumor cells. The VA mutants are also propagated normally in cells that do not respond to infection with PKR-inducing adenovirus.

The mutations of VA RNAs of this invention may affect the VAI and VAII genes. Alternatively or simultaneously, the mutations may affect the promoters of the VAI or VAII genes or their transcription termination sequences to block their expression.

VA mutant adenoviruses are propagated and amplified in cell lines with the active Ras pathway such as the human